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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/125,460	08/19/1998	HERMAN WALDMANN	1283-36	7809

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EXAMINER
HELMS, LARRY RONALD

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 11/12/2002

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/125,460	WALDMANN ET AL.	
	Examiner	Art Unit	
	Larry R. Helms	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 September 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18 and 26-72* is/are pending in the application.

4a) Of the above claim(s) *18,71 and 72* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26-70* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Election/Restrictions

1. Applicant's election of Group II, claims 26-70 in Paper No. 28 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. Claims 18, 71-72 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention. Election was made **without** traverse in Paper No. 28.

3. Claims 26-70 are under examination.

4. All previous rejections are moot in view of the election of a method as opposed to the products.

Specification

5. The disclosure is objected to because of the following informalities:

The use of the trademark "campath-1" has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 26-70 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 26-70 are indefinite for reciting that the non-cell binding antibody has reduced affinity in claims 26, 43, and 64 or the affinity for antigen is reduced to 50%, 10%, or 1% in claims 30-32 because the exact meaning of the phrases are unclear. It is unclear how a non-cell binding antibody can still have affinity for an antigen. Does the antibody still bind antigen or not?

b. Claim 59 contains the trademark/trade name "Campath-1". Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or

trade name. In the present case, the trademark/trade name is used to identify/describe a humanized antibody and, accordingly, the identification/description is indefinite.

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claim 59 is rejected under 35 U.S.C. § 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention, because the specification does not provide evidence that the claimed biological materials are (1) known and readily available to the public; (2) reproducible from the written description.

It is unclear if a cell line which produces an antibody having the exact chemical identity of Campath-1 is known and publicly available, or can be reproducibly isolated without undue experimentation. Therefore, a suitable deposit for patent purposes is suggested. Without a publicly available deposit of the above cell line, one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed. Exact replication of: (1) the claimed cell line; (2) a cell line which produces the chemically and functionally distinct antibody claimed; and/or (3) the claimed antibody's amino acid or nucleic acid sequence is an unpredictable event.

For example, very different V_H chains (about 50% homologous) can combine with the same V_K chain to produce antibody-binding sites with nearly the same size, shape,

antigen specificity, and affinity. A similar phenomenon can also occur when different V_H sequences combine with different V_K sequences to produce antibodies with very similar properties. The results indicate that divergent variable region sequences, both in and out of the complementarity-determining regions, can be folded to form similar binding site contours, which result in similar immunochemical characteristics. [FUNDAMENTAL IMMUNOLOGY 242 (William E. Paul, M.D. ed., 3d ed. 1993)]. In addition the entire campath-1 antibody is required to practice the invention not just the light and heavy chains. Therefore, it would require undue experimentation to reproduce the claimed antibody species Campath-1. Deposit of the hybridoma would satisfy the enablement requirements of 35 U.S.C. § 112, first paragraph. See, 37 C.F.R. 1.801-1.809.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claims 26, 31-32, 54-57, 63-65 are rejected under 35 U.S.C. 102(b) as being anticipated by Isaacs et al (Therapeutic Immunology 1:303-312, 1994, IDS #5).

The claims recite a method of producing a non-cell binding antibody wherein the method comprises identifying amino acid residues of a therapeutic antibody that are involved in antigen binding and modifying the residue(s) wherein the non-cell binding

antibody has reduced affinity for antigen and comprises at least one epitope which induces an immune response and induces immunological tolerance to the therapeutic antibody. Further claimed is wherein the affinity is reduced to 1% or less, wherein the modification comprises a single or double substitution in VH CDR2 and wherein each modified amino acid reduces the affinity, and fragmenting the therapeutic antibody. For this rejection the phrase "immunological tolerance" is interpreted to be therapeutic unresponsiveness and "fragmenting" is interpreted to mean any alteration of structure of the antibody.

Isaacs et al teach a method of producing a non-cell binding antibody comprising an H chain or an L chain paired with an irrelevant partner chain of a therapeutic antibody to CD4 and 8 (see page 304). The antibodies are useful for generating a therapeutic unresponsiveness to the therapeutic antibody (see abstract). It is inherent that since the antibodies have an irrelevant heavy or light chain they would not bind antigen thus meeting the reduction of affinity to less that 1%. In addition since the light chain is paired with an irrelevant heavy chain the modification is in CDR2 of the VH thus meeting the limitations of claims 54-57 and in addition claim 56 contains the term "comprises" which can be more than a double mutation and claim 57 depends on claim 56 and can be in more than one CDR besides CDR2 of the VH and the antibody was "fragmented" by altering the heavy or light chain.

Claim R j ctions - 35 USC § 103

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

13. Claims 26-70 are rejected under 35 U.S.C. 103(a) as being unpatentable over Isaacs et al (Therapeutic Immunology 1:303-312, 1994, IDS #5) as applied to claims 26, 31-32, 54-56, 63-65 above, and further in view of Carter et al (U.S. Patent 6,054,297, CON to 1992) and Riechmann et al (Nature 332:323, 1988, IDS #5).

Claims 26, 31-32, 54-56, 63-65 have been described supra. The other claims recite wherein the residues are identified by computer modeling, the residues are altered by site-directed mutagenesis, wherein the non-cell binding antibody has greater than 99% sequence identity to the therapeutic antibody and greater than 99% identity in the variable domain, framework regions, and constant region or identical in constant region, and the method comprises fragmenting the non-cell binding antibody to a Fab, single chain, the method further comprises expression and recovering the non-cell binding antibody, wherein the antibody is a humanized campath-1 antibody wherein the therapeutic antibody binds CD52, wherein the non-cell binding antibody comprises non-CDR regions of human origin and foreign CDRs, wherein the non-cell binding antibody is not a mixed molecule.

Isaacs et al has been described. Isaacs et al does not teach antibody fragments, humanized Campath-1, methods of site-directed mutagenesis, variable domains, frameworks, and constant regions of greater than 99%, or basically the therapeutic antibody is a humanized antibody. These deficiencies are made up for in the teachings of Carter et al and Riechmann et al.

Carter et al teach production of humanized antibodies, fragments of antibodies (column 8) and three dimensional models to identify residues that are involved with antigen binding and are responsible for affinity in a positive as well as negative sense and in some instances the effect of decreased binding might be desired and CDR residues are directly and most substantially involved and influence antigen binding (see column 9, lines 35-60).

Riechmann et al teach humanized Campath-1.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a non-cell binding antibody for inducing therapeutic unresponsiveness to a therapeutic antibody as taught by Isaacs et al in view of the well known methods of humanization and alteration in the antigen binding sites of antibodies as taught by Carter et al and use the Campath –1 antibody as taught by Riechmann et al.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a non-cell binding antibody for inducing therapeutic unresponsiveness to a therapeutic antibody as taught by Isaacs et al in view of the well known methods of humanization and alteration in the antigen binding sites of antibodies as taught by Carter et al and use the Campath –1 antibody as taught by Riechmann et because Isaacs et al teach a method of producing a non-cell binding antibody of a therapeutic antibody and the antibody does not bind antigen and the antibody was altered so as to reduce the affinity and to generate therapeutic unresponsiveness. It would have been obvious to alter the antigen binding ability of the antibody in view of Carter et al who teaches alteration of the CDRs can result in altered antigen binding and the method of Carter et al would result in minimal changes to the humanized antibody to result in reduced antigen binding. In addition, One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a non-cell binding antibody for inducing therapeutic unresponsiveness to a therapeutic antibody as taught by Isaacs et al in view of the well

known methods of humanization and alteration in the antigen binding sites of antibodies as taught by Carter et al and use the Campath –1 antibody as taught by Riechmann et al because Riechmann et al teach the humanized anti-campath-1 antibody can be used for therapy and to circumvent the anti-globulin response the Campath-1 antibody can be changed by altering the hypervariable regions and alteration may focus the response directly onto the binding site (see page 327). Thus, it would be obvious to focus on the CDRs which are the binding site of the antibody. Moreover, it would have been obvious to alter the CDR regions of the therapeutic antibody in order to produce a non-cell binding antibody in view of the teachings Isaacs et al of non-binding antibodies for unresponsiveness and in view of the well known method of altering the CDRs of an antibody to alter affinity as taught by Carter et al. Antibody fragments would also be obvious because it is known that fragments lacking the Fc region are better tolerated in therapy and have altered clearance rates. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Conclusion

14. No claim is allowed.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (703) 306-5879. The examiner can normally be reached on Monday through Friday from 7:00 am to 4:30 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

16. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 308-4242.

Respectfully,

Larry R. Helms Ph.D.

703-306-5879